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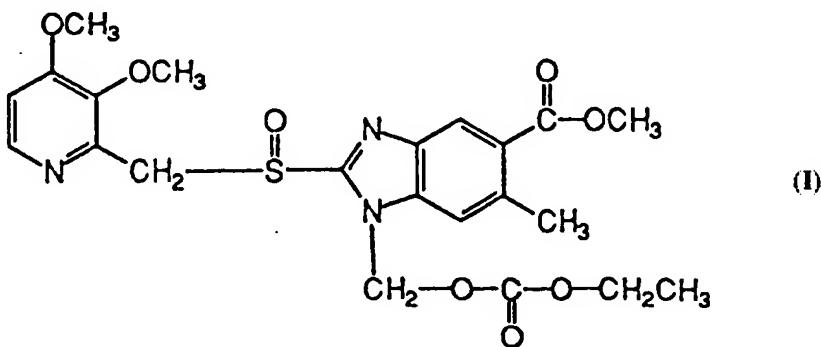


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(54) Title: SUBSTITUTED BENZIMIDAZOLE, PROCESSES FOR ITS PREPARATION AND ITS PHARMACEUTICAL USE



(57) Abstract

Novel compounds of formula (I) which inhibit exogenously or endogenously stimulated gastric acid secretion, processes for the preparation thereof and pharmaceutical compositions containing the compounds as active ingredient as well as the use of the compounds in pharmaceutical preparations, and new intermediates obtained.

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**SUBSTITUTED BENZIMIDAZOLE, PROCESSES FOR ITS
PREPARATION AND ITS PHARMACEUTICAL USE
DESCRIPTION**

5 **Field of the invention**

The object of the present invention is to provide novel, stable compounds, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of peptic ulcer. Furthermore the novel compounds may be used in the treatment of psoriasis and the treatment of Helicobacter infections.

10 The invention also relates to the use of the novel compounds in medicine, to pharmaceutical compositions containing said compounds as therapeutic ingredient. In a further aspect, the invention relates to processes for preparation of the new compounds, new intermediates and the use of the active compounds for the preparation of pharmaceutical compositions for the medical use indicated above.

15 It is a specific primary object of the invention to provide compounds with a good solid state stability and a high level of bioavailability. The compounds of the invention shall also exhibit good stability properties at neutral and acidic pH, a good potency in regard to inhibition of gastric acid secretion and shall not block the uptake of iodine into the thyroid gland.

20

Prior art and background of the invention

Different benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in numerous patent documents. Among these can be mentioned the compound 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole, generic name omeprazole, disclosed in EP 5129, and its single enantiomers. The isomeric mixture of the compounds 5-carbomethoxy-6-methyl-2-((3,4-dimethoxy-2-

pyridinyl)methyl)sulfinyl)-1*H*-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1*H*-benzimidazole-1-ylmethyl ethyl carbonate is described in the International Appl. WO 91/19711. The compounds 5 being sulfoxides, have an asymmetric center in the sulfur atom, i.e. exist as two optical isomers (enantiomers). The compounds disclosed in said International Patent Application inhibit exogenously or endogenously stimulated gastric acid secretion and are useful in the prevention and treatment of peptic ulcer.

10

It is desirable to obtain compounds with an improved and reproducible stability, especially in the solid state, to further enhance the usefulness of this type of drugs. A high and reproducible stability in the solid state is especially requested for storage purposes. A compound with such a 15 high solid state stability would also be easier to handle (use) in the preparation of pharmaceutical formulations. A high bioavailability, a high potency in inhibiting gastric acid secretion and also a high chemical stability at neutral and acidic pH are still desired.

20 Furthermore, it is desirable to obtain the pure isomeric compound in the form of its single enantiomers with respect to improved pharmacokinetic and metabolic properties of such compounds.

25 There is no examples given in prior art of the isolated and characterized compounds of the invention.

Outline of the invention

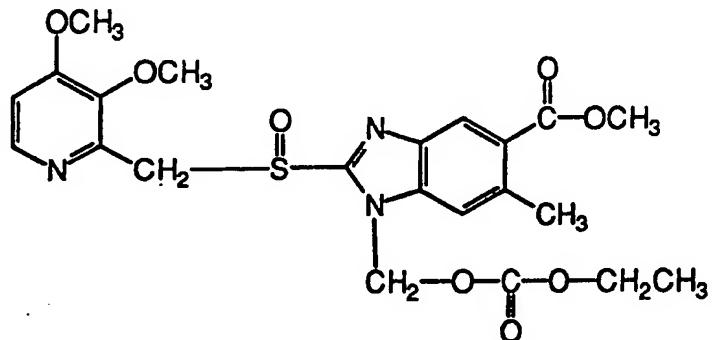
The compounds of the invention are effective as inhibitor of gastric acid secretion in mammals including man and do not block the uptake of 30 iodine into the thyroid gland.

It is unexpectedly found that the new compounds, i.e. the pure isomeric

compound or its single enantiomers, show a higher chemical stability in the solid state compared to the isomeric mixture making the compounds especially useful in the preparation of pharmaceutical formulations. It has also been found that the new compounds show high bioavailability
5 and exhibit a high chemical stability also at acidic pH making the compounds useful for non-enteric coated peroral formulations.

The compounds of the invention are 5-carbomethoxy-6-methyl-2-((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl
10 ethyl carbonate and its single enantiomers of the formula Ia and Ib.

15



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Ia (+)-enantiomer

Ib (-)-enantiomer

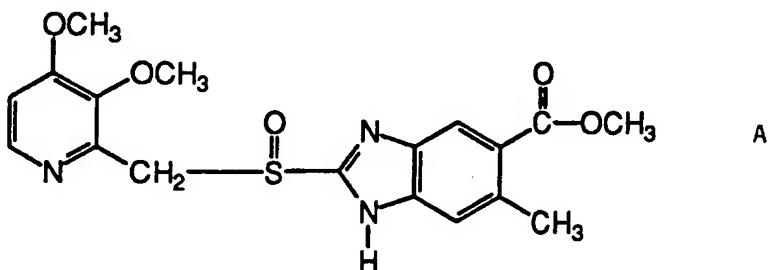
The compound of the invention has an asymmetric centre in the sulfur atom, i.e. exists as two optical isomers (two enantiomeric forms). The two pure enantiomeric forms (Ia, Ib), the racemic mixture as well as unequal mixtures of the two are within the scope of the present invention.
25

The compounds are substantially free from 6-carbomethoxy-5-methyl-2-((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate or its single enantiomers. Further, the optically pure (+)-5-carbomethoxy-6-methyl-2-((3,4-dimethoxy-2-

pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate, hereinafter called the (+)-5-isomer, is substantially free from the corresponding (-)-5-isomer and the opposite.

5 It is believed that the compounds of the invention are metabolized into the corresponding compounds, carrying H in the N-1 position, (compound A) before exerting its effect.

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The present invention also relates to the use of the compounds of the invention for inhibiting gastric acid secretion in mammals including man. In a more general sense, the compounds of the invention may be used for prevention and treatment of gastrointestinal inflammatory diseases, and 20 gastric acid-related diseases in mammals including man, such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis, and Zollinger-Ellison syndrome. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with 25 gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compounds of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, 30 especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout. Furthermore the compounds of the invention may be useful in the treatment of

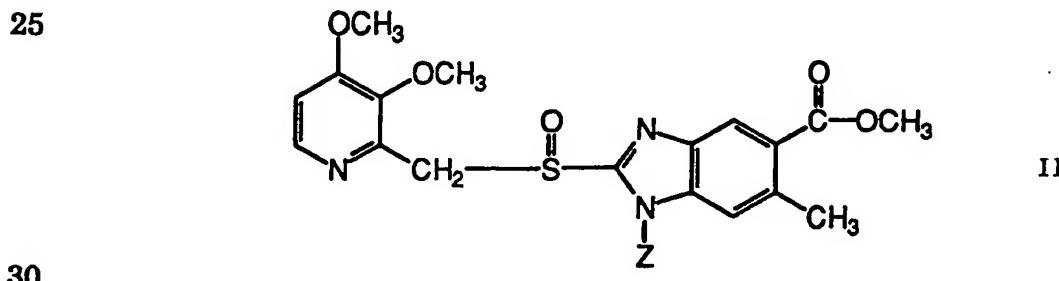
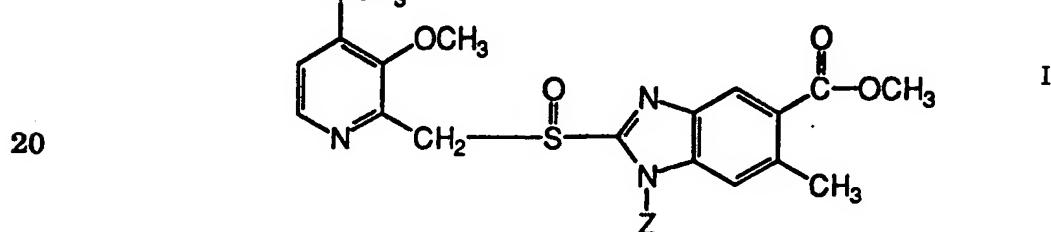
psoriasis as well as in the treatment of Helicobacter infections.

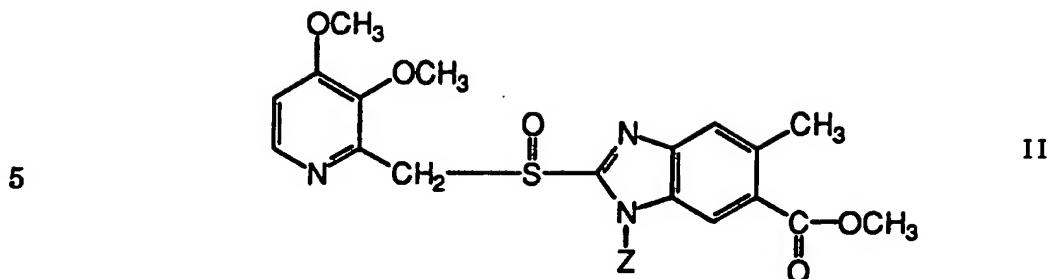
The invention also relates to pharmaceutical compositions containing the compounds of the invention, as active ingredient. In a further aspect, the
5 invention relates to processes for preparation of the new compounds, new intermediates and the use of the active compounds for the preparation of pharmaceutical compositions for the medical use indicated above.

Preparation

10 The compounds of the invention may be prepared according to one of the following methods a, b or c:

a) Reacting a compound of the formula I or its single enantiomers or an isomeric mixture of the two compounds of the formula II or their
15 single enantiomers

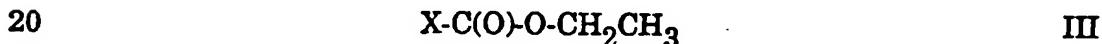




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wherein Z is either a metal cation such as Na^+ , K^+ , Li^+ or Ag^+ or a quaternary ammonium ion, such as tetrabutylammonium, with chloromethyl ethyl carbonate.

15 b) Reacting a compound of the formula I or its single enantiomers or an isomeric mixture of two compounds of the formula II or their single enantiomers, wherein Z is hydroxymethyl with a compound of the formula III,



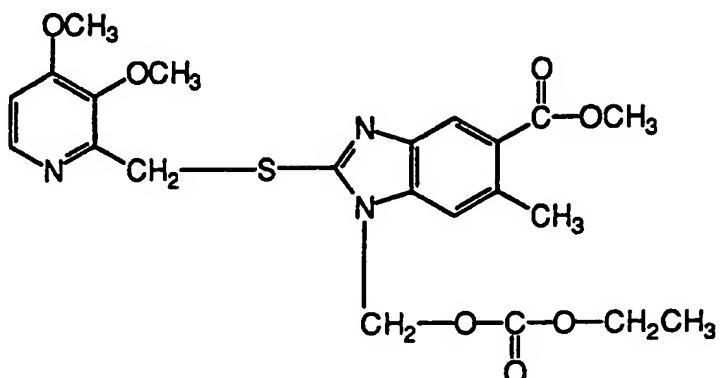
wherein X is Cl or imidazole or p-nitrophenoxy or a functionally equivalent group, in the presence of a suitable base such as triethylamine.

25

The reactions according to a) and b) are suitably carried out under protective gas in the absence of water. Suitable solvents are hydrocarbons such as toluene or benzene or halogenated hydrocarbons such as methylene chloride or chloroform or acetone, acetonitrile or 30 dimethyl-formamide. The reactions may be carried out at a temperature between the ambient temperature and the boiling temperature of the reaction mixture.

c) Oxidizing a compound of the formula IV or an isomeric mixture of two compounds of the formula V,

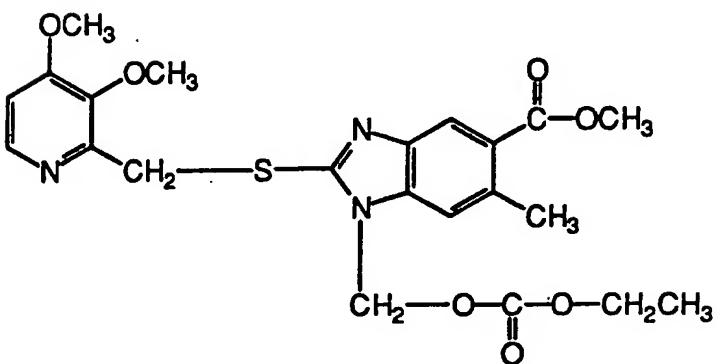
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IV

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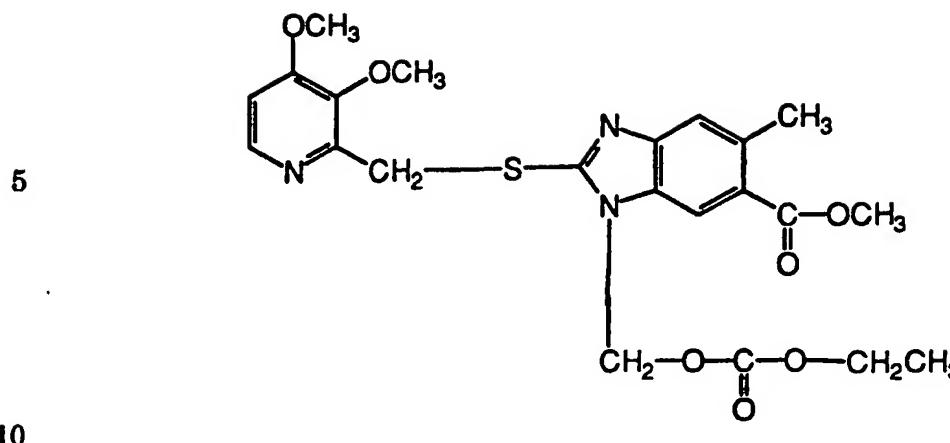


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V

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This oxidation may be carried out by using an oxidizing agent such as
 15 nitric acid, hydrogen peroxide, (optionally in the presence of vanadium compounds), peracids, peresters, oxone, oxaziridines, ozone, dinitrogentetraoxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, t-butylhypochlorite, diazabicyclo-[2.2.2]-octane bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, cericammonium nitrate, bromine, chlorine, and sulfuryl chloride. The oxidation usually takes place in a solvent such as halogenated hydrocarbons, alcohols, ethers, ketones.

The oxidation may also be carried out enzymatically by using an
 25 oxidizing enzyme or microbiologically by using a suitable microorganism.

When mixtures of structural isomers are obtained in any of the above methods, the compounds of the invention is isolated by means of crystallization or chromatography.

30

The expressions "pure isomeric compound" and "substantially free from" are used with the intention that the compounds of the invention shall

have a purity which is sufficient according to stability, preferably the compounds of the invention should have a purity of more than 90%, preferably more than 97%.

5 In some cases the starting materials utilized in the methods a) - c) are unknown. These unknown starting materials may be obtained from known compounds by utilizing processes known per se.

Chloromethyl ethyl carbonate may be obtained from ethanol by
10 treatment with chloromethyl chloroformate in the presence of pyridine.

Intermediates of formula I and II, wherein Z is hydroxymethyl are obtained by reaction of the corresponding benzimidazole compounds carrying H in the N-1 position with formaldehyde.

15 Starting materials of the formula III may be obtained by known methods, e.g. from ethanol by treatment with phosgene or 1,1'-carbonyl diimidazole or p-nitrophenyl chloroformate.

20 Starting materials of formula I and IV can be obtained from the isomeric mixtures of formula II and V by means of crystallization or chromatography.

For clinical use the compound of the invention is formulated into
25 pharmaceutical formulations for oral, rectal, or other modes of administration. The pharmaceutical formulation contains the compound of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, and between 1-50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch,

5 amylopectin, cellulose derivatives, gelatin, or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like, as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes.

10 The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalyzed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g.

15 beeswax, shellac or anionic film-forming polymers such as cellulose acetate phthalate, hydroxypropyl-methylcellulose phthalate, partly methyl esterified methacrylic acid polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different

20 active compounds or with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of an active compound of the invention, vegetable oil, fat, or

25 other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above. Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose,

30 sorbitol, mannitol, potato starch, amylopection, cellulose derivatives or gelatine. The hard gelatine capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil,

5 paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a dry micro enema, or they may be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents,

10 saccharine and carboxymethyl cellulose or other thickening agents.

Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

15 The typical daily dose of the active substance will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral dosages will be in the range of 5 to 500 mg per day of active substance.

20 The invention is illustrated by the following example.

Example 1.

Preparation of 5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate

25 2-Phenylsulfonyl-3-(4-nitrophenyl)oxaziridine (707 mg, 2.3 mmol) was

12

added into a solution of 5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole-1-ylmethyl ethyl carbonate (1.0 g, 2.1 mmol) in methylene chloride (20 ml).

The mixture was stirred at room temperature overnight and evaporated 5 to dryness. Column chromatography (silica gel, EtOAc/hexane) gave the crude compound (800 mg). Re-crystallization from ethanol gave the title compound (97% isomeric purity according to chromatographic analysis and 98% in NMR analysis). Yield 610 mg (59%).

¹H NMR (300MHz)

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1.29 (t,3H), 2.76 (s,3H), 3.89 (s,3H), 3.90 (s,3H), 3.92 (s,3H), 4.24 (q,2H), 4.97 (q,2H), 6.50 (q,2H), 6.78 (d,1H), 7.49 (s,1H), 8.14 (d,1H) and 8.40 (s,1H).

15 Example 2.

Preparation of (+)-5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate

20 (+)-5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole 4.6 g (12 mmol) was mixed with potassium carbonate 2.0 g (14 mmol) in acetonitrile (200 ml). Chloromethyl ethyl carbonate 1.8 g (13 mmol) was added together with acetonitrile (100 ml). The resultant mixture was stirred at ambient temperature for 14 h and 25 then the solvent was removed on a rotavapor. The residue was partitioned between water (100 ml) and methylene chloride (200 ml). The organic layer was separated, dried over Na₂SO₄ and then removed to give 5.3 g crude oily residue. The ratio of regioisomers in the crude product was 65:35 in favour of the desired component. Crystallisation 30 from ethyl acetate (50 ml), freshly treated with NH₃(g), afforded 0.66 g of a white solid contaminated with 5% of the undesired regioisomer. The product was dissolved in methylene chloride and the solution was

immediately evaporated. The residue was treated with ethyl acetate (10 ml) to give 0.43 g (7%) of the desired product in the form of a white solid, m.p. 148°-151°C. Chromatographic analysis (chiral AGP) showed that the product consisted of less than 1% of the undesired regioisomer and less
5 than 1% of the undesired stereoisomer.
[α]D + 130.3° (c=1% chloroform).

NMR data are given below.

10 Example 3.

Preparation of (-)-5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate

15 (-)-5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole 0.93 g (2.4 mmol) was mixed with potassium carbonate 0.40 g (2.9 mmol) in acetonitrile (50 ml). Chloromethyl ethyl carbonate 0.37 g (2.6 mmol) was added together with acetonitrile (25 ml). The resultant mixture was stirred at ambient temperature for 14 h and
20 then the solvent was removed on a rotavapor. The residue was partitioned between water (25 ml) and methylene chloride (50 ml). The organic layer was separated, dried over Na₂SO₄ and then removed to give 1.0 g crude oily residue. The ratio of regioisomers in the crude product was 65:35 in favour of the desired component. Crystallisation
25 from ethyl acetate (10 ml), freshly treated with NH₃(g), afforded 0.21 g of a white solid contaminated with 5% of the undesired regioisomer. The product was dissolved in methylene chloride and the solution was immediately evaporated. The residue was treated with ethyl acetate (5 ml) to give 0.10 g (9%) of the desired product in the form of a white solid,
30 m.p. 148°-151°C. Chromatographic analysis (chiral AGP) showed that the product consisted of less than 1% of the undesired regioisomer and less than 1% of the undesired stereoisomer.

[α]_D-131.6° (c=1%, chloroform).

NMR data are given below.

5 Ex. Solvent NMR data δ ppm

2 CDCl₃ 1.28 (t,3H), 2.75 (s, 3H), 3.88 (s, 3H), 3.90 (s,3H), 3.91 (s,
300 MHz 3H), 4.23 (q, 2H), 4.88-5.07 (AB-system, 2H), 6.44-6.54
(AB-system, 2H), 6.78 (d, 1H), 7.48 (s, 1H), 8.13 (d, 1H),
10 8.39 (s,1H).

3 CDCl₃ 1.29 (t, 3H), 2.76 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s,
300 MHz 3H), 4.23 (q, 2H), 4.89-5.07 (AB-system, 2H), 6.45-6.55
(AB-system, 2H), 6.78 (d, 1H), 7.49 (s, 1H), 8.14 (d, 1H),
15 8.40 (s, 1H).

Preparation of intermediates

Example A.

20

Preparation of 5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole-1-ylmethyl ethyl carbonate

To a suspension of 5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (8.5 g, 23 mmol) in acetonitrile (100ml) were added K₂CO₃ (6.3 g, 46 mmol) and then chloromethyl ethyl carbonate (3.5 g, 25 mmol). The mixture was stirred overnight. More chloromethyl ethyl carbonate (1.0 g) was added. The mixture was in total stirred for 48 h and then evaporated to dryness. Methylene chloride (300 ml) and water (100 ml) were added to the residue. Methylene chloride layer was separated, dried (MgSO₄) and evaporated. Crude product mixture (10.8 g) was obtained.

The title compound was purified by re-crystallizations from ethanol. Most of the by-products (6-carbomethoxy-5-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole-1-ylmethyl ethyl carbonate and an intermediate compound) were first crystallized out and the majority of
5 the title compound was left in mother-liquor. When the title compound in the mother-liquor was enriched to ca 85% in the mixture, the mother-liquor was evaporated to dryness. The title compound (96% isomeric purity according to NMR analysis) was obtained by a couple of re-crystallizations of the residue from ethanol. Yield 1.35 g (12%).

10

¹H NMR (300MHz)

1.28 (t,3H), 2.71 (s,3H), 3.91 (s br,9H), 4.21 (q,2H), 4.83 (s,2H),
6.08 (s,2H), 6.78 (d,1H), 7.32 (s,1H), 8.20 (d,1H), and 8.29 (s,1H).

15

Example B.

Preparation of (+)-5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

20

The crude product of the diastereomers of a mixture of two regiosomeric mandelic esters, namely 5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole (1.8 g, 3.3 mmol) was divided into three parts. Each part was chromatographed on a reversed phase column (HPLC, Kromasil C8) in order to separate the diastereomers. The stereoisomers were easily separated by elution with a mixture of aqueous 0.1 M ammonium acetate
25 and acetonitrile (70/30), but each separated diastereomer consisted of a mixture of the two regiosomers. These intermediates were used directly in their solutions during the hydrolyses; To the acetonitrile/aqueous
30

solutions of the more lipophilic diastereomer were added 1 M aqueous solutions of NaOH until the pH was around 12-13. After 5 minutes the solutions were neutralized with 3.0 M aqueous solutions of NH₄Cl. The solutions from each preparation were combined and extracted with 5 methylenechloride whereupon the organic phases were dried over Na₂SO₄. Removal of the solvents and flash chromatography of the residue (silica gel, methanol-methylenechloride gradient 1-8%) yielded 250 mg of a yellow oil. The product was crystallised by adding acetonitrile (3 ml) and after filtration there was obtained 210 mg (32%) 10 of the title compound as white crystals m.p. 171-173°C. [α]²⁰D = +153.1° (c=0.5%, chloroform).

Example C.

15 **Preparation of (-)-5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole**

To the acetonitrile/aqueous solutions of the less lipophilic diastereomer of 5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]-^(R/S)-20 sulfinyl]-1-[^(R)-mandeloyloxymethyl]-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]-^(R/S)-sulfinyl]-1-[^(R)-mandeloyloxymethyl]-1H-benzimidazole (obtained from the very same reversed phase chromatographic preparations described in Example B) were added 1.0 M NaOH until the pH was around 12-13. 25 After 5 minutes the solutions were neutralized with 3.0 M aqueous solutions of NH₄Cl. The solutions from each preparation were combined and extracted with methylenechloride whereupon the organic phases were dried over Na₂SO₄. Removal of the solvents and flash chromatography of the residue (silica gel, methanol-methylenechloride gradient 1-8%) yielded 270 mg of a yellow oil. The product was 30 crystallized by adding acetonitrile (3 ml) and after filtration there was obtained 210 mg (32%) of the title compound as white crystals m.p. 173-

174°C.

$[\alpha]^{20}_D = -150.0^\circ$ (c = 0.5%, chloroform).

Example D.

5 Preparation of 5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]-
 (R/S)-sulfinyl]-1-(R)-mandeloyloxymethyl-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]-
 (R/S)-sulfinyl-1-(R)-mandeloyloxymethyl-1H-benzimidazole

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A solution of 0.33 g (8.2 mmol) sodium hydroxide in 1.6 ml water was added to a mixture of 1.4 g (4.1 mmol) tetrabutylammonium hydrogen sulfate and 0.62 g (4.1 mmol) of (R)-(-)-mandelic acid. Chloroform (50 ml) and a mixture of 5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]-sulfinyl]-1-(chloromethyl)-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-(chloromethyl)-1H-benzimidazole (as racemates) were added and the mixture was refluxed for 3 hours. The reaction mixture was chilled and then partitioned between ethyl acetate and water. The layers were separated and the organic phase was washed with water and dried over Na_2SO_4 . Removal of solvents yielded a diastereomeric mixture of the two regioisomeric mandelic esters. The crude product was used directly in the chromatographic step where the diastereomers were separated (Examples B and C). Yield: 2.4 g, 62%.

25

Biological Effects

Bioavailability

Bioavailability, is assessed by calculating the quotient between the areas under blood/plasma concentration (AUC) curve of the compound A following 1) intraduodenal (id) or oral (po) administration of the compound of the invention and 2) intravenous (iv) administration of

compound A, form the rat and the dog. Low, therapeutically relevant doses, were used. Data are provided in Table I.

Potency for inhibition of acid secretion

5 The potency for inhibition of acid secretion is measured in the female rat, oral administration and in the dog, oral administration.

Potency data are provided in Table I.

Effects on the uptake of iodine into the thyroid gland.

10 The effect of the compound of the invention on the uptake of iodine into the thyroid gland is measured as an effect on the accumulation of ^{125}I in the thyroid gland of the compound A, that is the active compound generated in the metabolism of the compound of the invention.

15 Biological tests

Inhibition of Gastric Acid Secretion in the Conscious Female Rat.

Female rats of the Sprague-Dawley strain are used. They are equipped with cannulated fistulae in the stomach (lumen), for collection of gastric 20 secritions. A fourteen days recovery period after surgery is allowed before testing is commenced.

Before secretory tests, the animals are deprived of food but not water for 20 h. The stomach is repeatedly washed through the gastric cannula, and 25 6 ml of Ringer-Glucose is given s.c. Acid secretion is stimulated with infusion during 2.5 h (1.2 ml/h, s.c) of pentagastrin and carbachol (20 and 110 nmol/kg h, respectively), during which time gastric secretions are collected in 30-min fractions. Test substance or vehicle are given orally 120 min before starting the stimulation, in a volume of 5 ml/kg.

30 Gastric juice samples are titrated to pH 7.0 with NaOH, 0.1 mol/L, and acid output is calculated as the product of titrant volume and concentration. Percentage inhibition was calculated from group mean

responses (n=6-10/group) and the ED₅₀-value was obtained from a graphical interpolation on the log dose-response curve. The results are based on acid output during the period 2.5-4.5 hours after dosing.

5 Bioavailability in the Male Rat.

Male adult rats of the Sprague-Dawley strain were used. 1-3 days, prior to the experiments, all rats were prepared by cannulation of the left carotid artery under anaesthesia. The rats used for the intravenous experiments, were also cannulated in the jugular vein. (Ref. V Popovic and P Popovic, J Appl Physiol 1960;15,727-728). The rats for the intraduodenal experiments, were also cannulated in the upper part of the duodenum. The cannulas were exteriorized at the nape of the neck. The rats were housed individually after surgery and were deprived of food, but not water, before administration of the test substance. The same dose (4 µmol/kg) were given iv and id as a bolus for about one minute (2 ml/kg).

20 Blood samples (0.1-0.4 g) were drawn repeatedly from the carotid artery at intervals up to 4 hours after given dose. The samples were frozen as soon as possible until analysis of the test compound.

The area under blood concentration vs time curve, AUC, for the compound A, determined by the linear trapezoidal rule and extrapolated to infinity by dividing the last determined blood concentration by the elimination rate constant in the terminal phase. The systemic bioavailability (F%) of the compound A following intraduodenal administration of compounds of the invention of formula I was calculated as

$$30 \quad F(\%) = \frac{AUC(\text{Compound A})_{\text{id}}(\text{compound of the invention})}{AUC(\text{Compound A})_{\text{iv}}(\text{Compound A})} \times 100$$

Inhibition of Gastric Acid Secretion and Bioavailability in the Conscious Dog

Harrier dogs of either sex were used. They were equipped with a duodenal fistula for the administration of test compounds or vehicle and a Heidenhain-pouch for the collection of gastric secretions. Before secretory tests the animals were fasted for about 18 h but water was freely allowed. Gastric acid secretion was stimulated by a continuous iv infusion (12 ml/h) of histamine dihydrochloride at a dose producing approximatively 80% of the individual maximal secretory response, and gastric juice collected in "consecutive" 30-min fractions. The duration of the histamine infusion was 6.5 hours. The test compound or vehicle were given orally, iv in a volume of 0.5 ml/kg. The time of administration was 1.5 hours after the start of the histamine infusion. In the case of oral administration, the compound was thus given directly into the acid secretory main stomach.

The acidity of the gastric juice samples were determined by titration to pH 7.0, and the acid output determined. Percentage inhibition was individually calculated with reference to acid output in control experiments with vehicle. These calculations were based on absolute or fractional rates of acid output. In the latter case, the acid output after administration of test compound or vehicle was expressed as fractions of the acid output immediately before the administration. ED₅₀-values were obtained by graphical interpolation of log dose-response curves with 2-3 dose levels and 2-4 dogs. The results are based on secretory responses 3 hours after dose.

Blood samples for the analysis of test compound concentration in plasma were taked at intervals up to 5 hours after dosing. Plasma was separated and frozen within 30 min after collection and later analyzed. AUC (area under the plasma concentration - time curve) from time zero to 5 hours

after dose for compound A, was calculated by the linear trapezoidal rule. The systemic bioavailability (F%) of the compound A after oral administration of compounds of the invention was calculated as described above in the rat model.

5

Effect on the accumulation of ^{125}I in the thyroid gland

The accumulation of ^{125}I in the thyroid gland was studied in male, Sprague-Dawley rats which were deprived of food for 24 hours before the test. The experimental protocol of Searle, CE et al. (Biochem J 1950; 10 47:77-81) was followed.

Test substance, suspended in 0.5% buffered (pH 9) Methocel, was administered by oral gavage in a volume of 5 ml/kg body weight. After 1 hour, ^{125}I (300 Bq/kg, 3 ml/kg) was administered by intraperitoneal injection. Four hours after ^{125}I -administration, the animals were killed by CO₂-asphyxiation and bled. The thyroid gland together with a piece of the trachea was dissected out and placed in a small test tube for the assay of radioactivity in a gamma counter (LKB-Wallac model 1282 Compugamma). Percentage inhibition was calculated according to the formula 100 (1-T/P), where T and P is the mean radioactivity of thyroid glands from animals treated with test agent and placebo (buffered Methocel), respectively. The statistical significance for a difference between test agent- and placebo-treated animals was assessed with the Mann-Whitney U-test (two-tailed). P<0.05 was accepted as significant.

25

Chemical stability

The chemical stability of the racemic mixture of the compound of the invention has been followed kinetically at low concentration at 37°C in aqueous buffer solution at different pH values. The results in Table 2 show the half life ($t_{1/2}$) at pH 7, that is the time period after which half the amount of the original compound remains unchanged and $t_{10}\%$ of pH 2, that is the time period after which 10% of the original compound has

decomposed.

The chemical stability in the solid state was tested. The degradation of the compound of the invention was followed by liquid chromatography.

5 The substance was stored as a crystalline material at 90°C or at 100°C and analysed after 6 and 14 days or after 2 days. The amount of by-products was evaluated as area per cent of the total peak area. The results are shown in Table 2.

10 Results of biological tests

Table 1 gives a summary of the test data available for the compounds of the invention.

Results of stability tests

15 Table 2 gives a summary of the test data available for the compounds of the invention, called "5-isomer", and related compounds disclosed in the prior art. Those related compounds are the isomeric mixture of 6-carbomethoxy-5-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and 5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]- sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate called "isomeric mixture" and 6-carbomethoxy-5-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, called "6-isomer". In the solid state stability test the amount of degradation products were measured after 8 and 14 days storage instead of 6 and 14 days as for the compound of the invention. As can be seen from Table 2 the compound according to the invention is the most stable compound. No degradation products could be detected after 14 days storage at 90°C for the compound of the invention "5-isomer", for the "isomeric mixture" more than 20% degradation products are formed during 14 days storage and for the "6-isomer" 20% degradation products are formed already after 8 days storage.

Further, the solid state stability has also been measured at 100°C. At this temperature approximately 20% degradation products are found already after 2 days storage in the "isomeric mixture" and in the "6-isomer". The compound of the invention had only a very slight increase
5 in the amount of by-products during storage at 100°C for 2 days.

Table 1. Biological Test Data

	Inhibition of acid secretion, oral		Bioavailability F %		Per cent inhibition of ¹²⁵ I-accumulation in the rat thyroid gland after oral administration of 400 µmol/kg
	Dog	Rat	Dog	Rat (oral)	
5					
ED₅₀		µmol/kg			
Dog	1.6	3.7	57	75	0

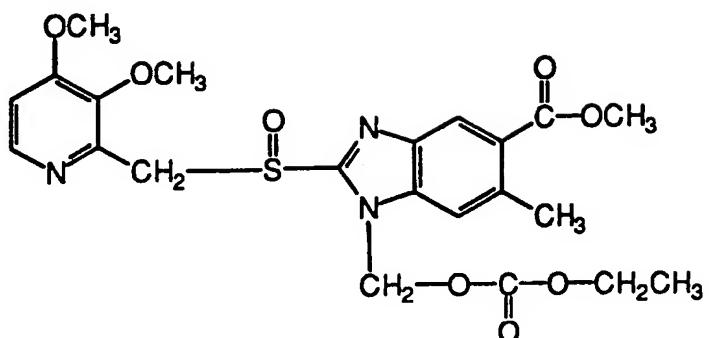
Table 2. Stability Data

<u>Test compound</u>	<u>Chemical stability</u> in solution at as area percent (90°C)				<u>Solid stability by products</u> as area percent (100°C)			
	pH 7	pH 2	t _{1/2} (h)	t 10% (h)	Day 0	Day 6	Day 8	Day 14
5								
The invention: "5-isomer"	91	17.7			4	3.1	-	3.4
Ref. "isomeric mixture"	87	13.1			4.5	-	18.1	28.1
10	Ref. "6-isomer"	50	10.5		1.1	-	21.6	-
					<u>Solid stability by-products</u> as area percent (100°C)			
15					Day 0	Day 2		
					0.8	1.0		
					0.9	19.4		
					0.7	22.6		

CLAIMS:

1. A compound having the formula

5



10

2. 5-carbomethoxy-6-methyl-2-((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate substantially free from 6-carbomethoxy-5-methyl-2-((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate.

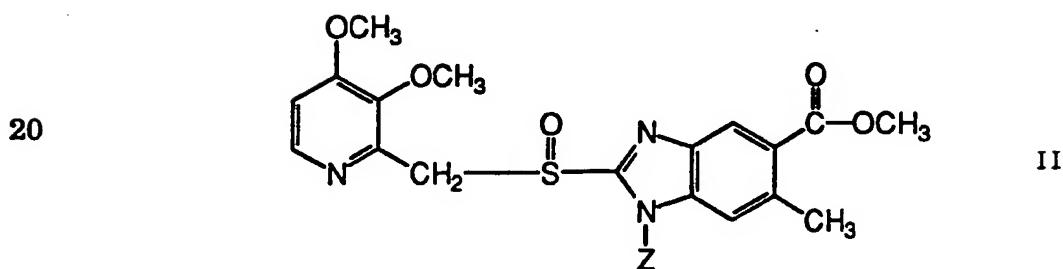
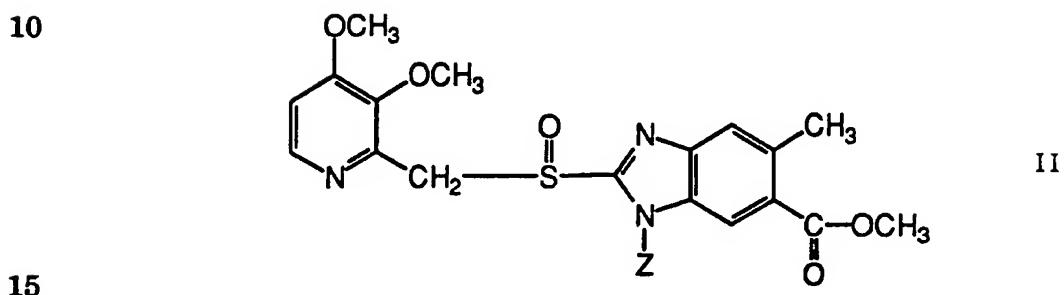
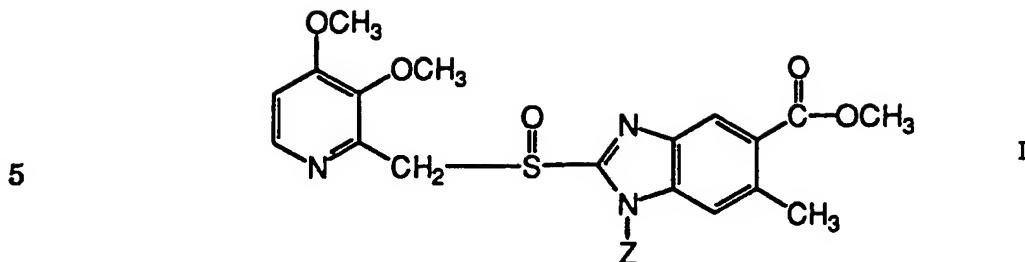
3. (+)-5-carbomethoxy-6-methyl-2-((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate.

4. (-)-5-carbomethoxy-6-methyl-2-((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate.

25 5. A process for the preparation of a compound according to claim 1 characterized by

a) reacting a compound of the formula I or its single enantiomers or an isomeric mixture of two compounds of the formula II or their single enantiomers,

30



25 wherein Z is either a metal cation such as Na⁺, K⁺, Li⁺ or Ag⁺ or a quaternary ammonium ion, such as tetrabutylammonium, with chloromethyl ethyl carbonate,

30 b) reacting a compound of the formula I or its single enantiomers or an isomeric mixture of two compounds of the formula II or their single enantiomers, wherein Z is hydroxymethyl with a compound of the formula III,

28



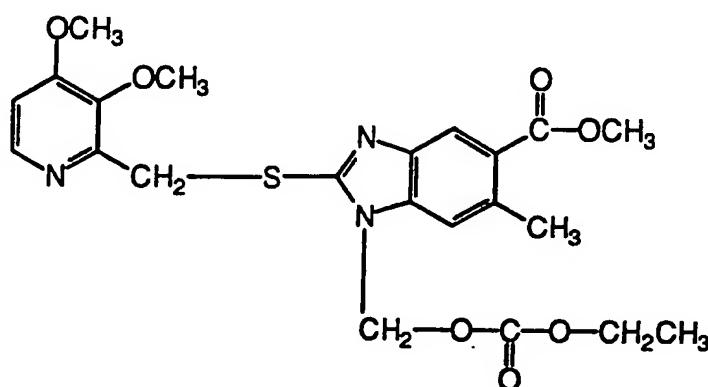
III

wherein X is Cl or imidazole or p-nitrophenoxy or a functionally equivalent group, in the presence of a suitable base such as
 5 triethylamine, or

c) oxidizing a compound of the formula IV or an isomeric mixture of two compounds of the formula V,

10

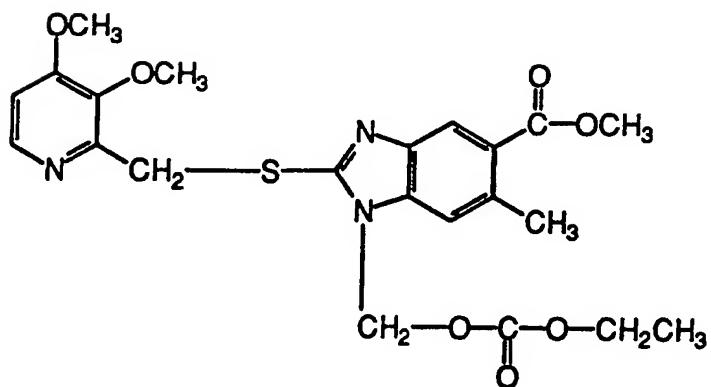
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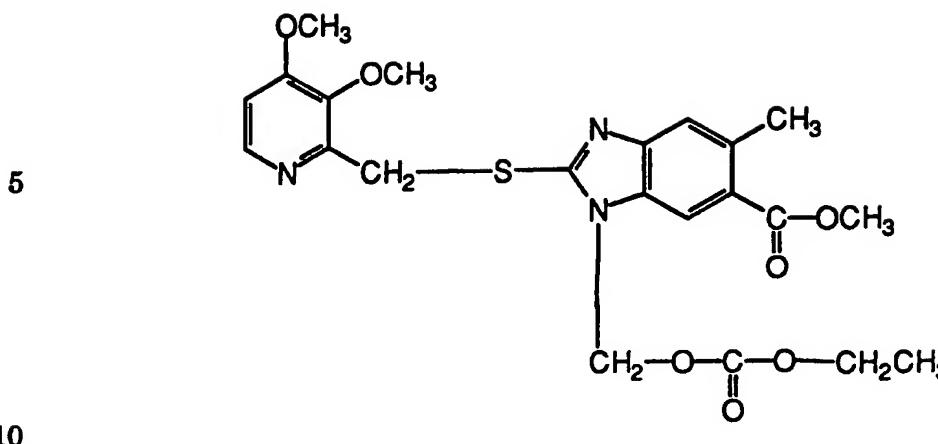
IV

30

25



V



15

and when mixtures of structural isomers are obtained in any of the above methods the pure isomeric compound is isolated by crystallisation or
20 chromatography.

6. A process according to claim 3, wherein the reactions according to a) and b) are carried out under protective gas and in the absence of water, and the oxidation according to c) is carried out in a solvent by using an
25 oxidizing agent.

7. A compound according to claim 1 for use in therapy.

8. A pharmaceutical composition containing the compound according to
30 claim 1 as an active ingredient.

9. A method for inhibiting gastric acid secretion by administration to

mammals including man in need of such treatment an effective amount of the compound according to claim 1.

10. A method for treatment of gastrointestinal inflammatory diseases
5 comprising administration to mammals including man in need of such treatment an effective amount of the compound according to claim 1.

11. Use of the compound according to claim 1 in the manufacture of a medicament for inhibiting gastric acid secretion in mammals including
10 man.

12. Use of the compound according to claim 1 in the manufacture of a medicament for treatment of gastrointestinal inflammatory diseases in mammals including man.

15

13. The compound 5-carbomethoxy-6-methyl-2[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/01093

A. CLASSIFICATION OF SUBJECT MATTER		
IPC6: C07D 401/12, A61K 31/44 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
IPC6: C07D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched SE,DK,FI,NO classes as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
CAS-ONLINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, A1, 9119711 (AKTIEBOLAGET ASTRA), 26 December 1991 (26.12.91), see example 1 --- -----	1-8,11-13
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search	Date of mailing of the international search report	
17 February 1995	06 -03- 1995	
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. + 46 8 782 25 00	

INTERNATIONAL SEARCH REPORT

Information on patent family members

31/12/94

International application No.

PCT/SE 94/01093

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9119711	26/12/91	AU-B-	649453 26/05/94
		AU-B-	649456 26/05/94
		AU-A-	8009791 07/01/92
		AU-A-	8061791 07/01/92
		CA-A-	2083606 21/12/91
		CA-A-	2083714 21/12/91
		CN-A-	1058212 29/01/92
		CN-A-	1058213 29/01/92
		EP-A-	0535081 07/04/93
		EP-A-	0593463 27/04/94
		HU-D-	9204033 00/00/00
		HU-D-	9204034 00/00/00
		NZ-A-	238546 25/03/94
		OA-A-	9682 15/05/93
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		WO-A-	9119712 26/12/91